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EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 03/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,341	BUMP ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/23/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *1-20,28-31 and 34-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-27,32 and 33* is/are rejected.

7)☒ Claim(s) *32* is/are objected to.

8)☒ Claim(s) *1-88* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01232004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and remarks, filed 12/23/03, are acknowledged. Amended claims 21-24, 26-27, and 32 are acknowledged.

Applicant's arguments, filed 12/23/03, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The information disclosure statement, filed 1/23/04, has been fully considered.

Claims 21-27 and 32-33 are herein under examination.

Claim Objections

Claim 32 is objected to because of the following informality: It fails to end in a period. Appropriate correction is required.

Claim Rejections – 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The

factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of the skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF SCOPE OF ENABLEMENT

The rejection of claims 21-27, 32, and 33 is maintained under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the atomic coordinates for residues 802-1124 of Tie-2 and Inhibitor III complex, does not reasonably provide enablement for the atomic coordinates of an unbound version of a Tie-2 polypeptide or atomic coordinates of the complete polypeptide of Tie-2 and Inhibitor III complex. The invention as presently stated in the claim 21 encompasses these additional sets of atomic coordinates, but they are not included in the specification which consequently causes a lack of scope of enablement of the instant invention for one of ordinary skill in the art.

The rejection is maintained and reiterated for reasons of record.

The specification states that Tie-2 may be present in various states, such as single or multiple-phosphorylated species. Although Applicants have disclosed information to enable one skilled in the art to make a diphosphorylated Tie-2 protein crystal of the space group $P2_12_12_1$ with unit cell dimensions a = 54.320 Å, b = 75.872 Å, c = 78.143 Å, and $\alpha = \beta = \gamma = 90.0°$ (page 10, lines 14-25 and page 48, lines 11-19), a catalytically inactive mutant of human Tie-

2/inhibitor crystal of a space group $C222_1$ with unit cell dimensions a = 75.195 Å, b = 116.287 Å, c = 95.060 Å, and $\alpha = \beta = \gamma = 90.0°$ (page 11, lines 1-2 and page 49, lines 24-25), and the crystal structures of three other crystals of Tie-2/ligand complexes, including a Tie-2/Inhibitor III complex, (page 11, line 3) of a space group P42212 with unit cell dimensions a = b = 86.0 Å, c = 112.0 Å, and $\alpha = \beta = \gamma = 90.0°$ (page 49, lines 26-28), the specification does not reasonably provide enablement for finding atomic coordinates of an unbound Tie-2 polypeptide as well as an entire Tie-2 polypeptide and Inhibitor III complex as encompassed in claim 21. The claim is broader than the enablement provided by the disclosure with regard to the atomic coordinate sets that could be used in the instant method claims. A method that relies on data from an unpredictable art such as protein crystallization would require clear and precise guidance for one skilled in the art to reliably use the said method. As the science of protein crystallization is well known to be a trial and error procedure with unpredictable results (Drenth, page 1, lines 13-20), one skilled in the art would require clear and precise guidance to make any particular crystal in order to obtain atomic coordinates to define active subsites. Accordingly, it would be very difficult for one of ordinary skill in the art to obtain atomic coordinates beyond those mentioned in the instant case where specific coordinates are disclosed. Due to the unpredictability and difficulty of crystallizing proteins, it is unlikely that one of skill in the art would be able to make another crystal relying solely on the information for the crystal disclosed in the specification without undue experimentation. Again, due to the unpredictability in the art, one of skill in the art could not reasonably expect to obtain the structural coordinates of an unbound Tie-2 protein or a complete Tie-2 polypeptide/Inhibitor III complex based on generic guidelines of making crystals without undue experimentation.

Applicants state that instant claim 21 is limited to obtaining the atomic coordinates of a crystal of a polypeptide comprising the catalytic domain of a Tie-2 protein, including specific residues as pointed out on page 10, lines 3-6. It is acknowledged that the coordinates from crystals as stated in the above paragraph are enabled. Applicants state the coordinates comprising the catalytic domain of a Tie-2 protein are the defining feature of the instant invention. It is noted that the way instant claim 21 is currently worded, step (a) broadly encompasses atomic coordinates of any crystal of a polypeptide comprising such a domain which includes more types the atomic coordinates sets of crystallized polypeptides than listed in instant application. Applicants only provide enablement for the atomic coordinates referred to in the instant application. Applicants submit that the Examiner states the instant specification is not enabling based on the amount of direction or guidance provided. It is noted that, as stated in the previous Office Action, enablement was provided for the atomic coordinates for residues 802-1124 of Tie-2 and Inhibitor III complex, but not for the atomic coordinates of an unbound version of a Tie-2 polypeptide or atomic coordinates of the complete polypeptide of Tie-2 and Inhibitor III complex, because the later atomic coordinates were not provided in the instant application. Due to the unpredictability of this art, Applicants are enabled only for the atomic coordinates specifically stated in the application. As stated in the MPEP § 2164.03:

> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.

A latter section of the MPEP § 2164.03 also states the following:
[I]n applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

Such unpredictability is present the art involving crystallization of proteins. Therefore, the lack of scope of enablement rejection set forth in the previous Office Action is maintained.

LACK OF WRITTEN DESCRIPTION

The rejection of claims 21-27, 32, and 33 is maintained under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of the invention was filed, had possession of the claimed invention.

The rejection is maintained and reiterated for reasons of record.

Claims 21-27, 32, and 33 are directed to a method involving atomic coordinates of crystalline Tie-2 proteins and a Tie-2/Inhibitor III. Crystals structure data are provided for a diphosphorylated Tie-2 protein crystal of the space group $P2_12_12_1$ with unit cell dimensions a = 54.320 Å, b = 75.872 Å, c = 78.143 Å, and $\alpha = \beta = \gamma = 90.0°$ (page 10, lines 14-25 and page 48, lines 11-19), a catalytically inactive mutant of human Tie-2/inhibitor crystal of a space group $C222_1$ with unit cell dimensions a = 75.195 Å, b = 116.287 Å, c = 95.060 Å, and $\alpha = \beta = \gamma =$ 90.0° (page 11, lines 1-2 and page 49, lines 24-25), and the crystal structures of three other

crystals of Tie-2/ligand complexes, including a Tie-2/inhibitor III complex, (page 11, line 3) of a space group P42212 with unit cell dimensions a = b = 86.0 Å, c = 112.0 Å, and $\alpha = \beta = \gamma = 90.0°$ (page 49, lines 26-28). Atomic coordinates are provided in Fig. 5A-5RR for the catalytic domain of Tie-2 (residues 802-1124) and inhibitor III complex (page 5, lines 5-15); however, atomic coordinates are not provided for the unbound Tie-2 polypeptide or for the entire Tie-2 polypeptide and inhibitor III complex which are encompassed in the "comprising" language used on line 3 of claim 21. Applicants have not sufficiently described these additional sets of atomic coordinates that can be used in the claimed methods in such full, clear, concise terms that an artisan of ordinary skill in the art would recognize Applicants were in possession of the claimed invention.

The specification discloses SEQ ID NO: 1 that corresponds to amino acid sequence of a Tie-2 protein. SEQ ID NO: 1 meets the written description provisions of 35 U.S.C. 112, first paragraph. Also, claim 27 gives sequence written basis for amino acid residues 802-1124. However, due to the open claim language of "comprises" in claim 27, this claim is directed to encompass amino acid sequences that do not meet the written description provision of 35 U.S.C. 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by this claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO: 1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more

than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only SEQ ID NO: 1, residues 802-1124 of SEQ ID NO: 1, and atomic coordinates found in Fig. 5A-5RR, but not the full breadth of the claims, meet the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicants state the Examiner has confused the issue by not treating written description separate and distinct from the enablement requirement. This is found unpersuasive as these two sections with 35 U.S.C. 112, first paragraph, have been separately addressed. Adequate description in some unpredictable arts, such as protein crystallization, do require substantial and sometimes literal support for the claimed invention. Applicants state the claim being examined in Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai

Pharmacentical Co. Ltd., 18 USPQ2d 1016 was directed to a DNA, whereas the instant application is directed to a method. However, it is noted that this method contains reference to a polypeptide so that the same general principle applies. Applicants state they are claiming a method so that the only written description requirement they must meet is providing adequate disclosure to allow another to practice the invention. This is found unpersuasive as the method involves crystal coordinates so that any crystal encompassed in the instant claims needs to fully meet the written description provisions of 35 U.S.C. 112, first paragraph. Applicants note in Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016, it was not necessary that the patent applicant test all the embodiments of his invention. This does not apply to unpredictable arts as stated in the MPEP § 2164.03:

[I]n applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

Applicants state in Fiddes v. Baird, 30 USPQ2d 1481, 1483 that claims were found unpatentable due to lack of written description for the broad class, but that claims in this issue related to a recombinant DNA molecule, while the instant claims involve a method. This is found unpersuasive as the method contains reference to a polypeptide so that the same general principle applies. Applicants state they are claiming a method so that the only written description requirement they must meet is providing adequate disclosure to show possession of the invention. This is found unpersuasive as the method involves crystal coordinates so that the atomic coordinates of any crystal encompassed in the instant claims need to fully meet the

written description provisions of 35 U.S.C. 112, first paragraph. Regarding University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405, Applicants state their claims are directed to a method, not to a DNA. However, the instant claims contain atomic coordinates from protein crystals and therefore Applicants must have for all atomic coordinates from protein crystals that are broadly encompassed in the instant claims in order to meet written description provisions due to the unpredictability of this art. Applicants state that written description is not required for the entire scope of the claims, only the invention. This is found unpersuasive as the claims define the invention, and therefore written description is required for the entire scope of the claims. Applicants state the patentee is not obligated to describe every possible embodiment of the invention. This does not apply to unpredictable arts as stated in the MPEP § 2164.03:

[I]n applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

Regarding the term "comprising" in instant claim 21, Applicants submit that the atomic coordinates of the catalytic domain are always present and that it is irrelevant whether other coordinates are present. This is found unpersuasive as the "comprising" language in instant claims 21 and 27 encompass atomic coordinates of other polypeptides besides those mentioned in the instant application which do not have written support in the instant application. These claims include polypeptides comprising such a domain (claim 21) and such amino acids (claim 27). In conclusion, Applicants only have written support for the atomic coordinates of polypeptides that are set forth in the instant application. Since the instant claims can be

reasonably and broadly interpreted to encompass other polypeptides or complexes, there is a lack of written description for the instant application.

Claims Rejected Under 35 U.S.C. § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 21-27, 32, and 33 is maintained under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The rejection is maintained and reiterated for reasons of record.

Claims 21-25 are vague and indefinite due to the unclarity of citing an abbreviation, such as Tie-2. Correction is suggested by amending in of the full name in parentheses. Claims 26-27, 32, and 33 are also rejected due to their direct or indirect dependence from claims 21 and 24. Applicants submit that Tie-2 is a well known term in the art by referring to a publication by Shawver et al. This is found unpersuasive as a single publication is evidence that a term is "known" in the art, but does not support the "well known" character of such a term. A well known term would be evidenced by a textbook citation of the term or a review article, or alternatively, at least a few publications from different sources.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 21, 22, and 26 is maintained under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (P/N 6,160,092), in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)).

The rejection is maintained and reiterated for reasons of record.

Chen et al. describe a method for identifying an agent that diminishes the activity of a protein (col. 4, lines 56-60). Chen et al. describe determining the three-dimensional structure of a compound based on structural coordinates obtained from X-ray crystallographic analysis of crystals (col. 4, lines 14-22). Chen et al. describe various binding domains of a protein (col. 6, lines 12-18 and col. 9, lines 56-64), interactive areas in these domains using crystal structure data (col. 10, lines 3-9) and catalytic sites (col. 14, lines 61-65). Chen et al. describe using computer modeling to select potential agents and contacting the agents with the protein (col. 4, col. 21-26). Chen et al. describe determining whether the agent affects the ability of the protein to induce

expression of a gene that is operably under the control of a promoter containing the binding site for the protein (col. 4, lines 56-50). Chen et al. describe the potential modulator can be synthesized de novo or selected from a library of chemicals (col. 23, lines 13-24). Chen et al. describe that the proteins and core fragments thereof may be chemically synthesized (col. 19, lines 21-24) and modified (col. 5, lines 38-39). Chen et al. describe identifying potential modulators by screening a random peptide library and further modified using computer modeling programs (col. 22, lines 51-59). Even though the method described by Chen et al. does not specify that the active site was identified by the crystal structure coordinates and the three-dimensional model of the Tie-2 protein and Tie-2/Inhibitor III complex, the specific limitations of crystal structure coordinates and the three-dimensional model of the Tie-2 protein and Tie-2/Inhibitor III complex in this instant case do not distinguish the invention from the prior art in terms of patentability, because they are nonfunctional descriptive subject matter.

In re Gulack defines nonfunctional descriptive material to be descriptive material that is not functionally related to the substrate, in such a way that this descriptive material will not distinguish the invention from the prior art in terms of patentability. Also, the MPEP indicates that descriptive material unable to exhibit any functional interrelationship with the way in which computing processes are performed does not constitute a statutory process, machine, manufacture or composition (MPEP § 2106, section VI). Due to the fact that the coordinate data set derived from the crystal structure of the Tie-2 protein or Tie-2/Inhibitor III complex to develop three-dimensional models in the instant case are merely stored so as to be read or outputted by a computer without creating any functional interrelationship, either as part of the stored data or as part of the computing processes performed by the computer, this descriptive

material alone does not impart functionality either to the data as structured, or to the computer. As the invention of Chen et al. contains a method for identifying agents that interact with a protein and various modifications to their invention would be apparent to one of ordinary skill in the art (col. 38, lines 2-5), an artisan of ordinary skill in the art would have been motivated to include any crystalline protein already identified into this method in order to search for new drugs (col. 3, lines 5-9). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the three-dimensional model of the Tie-2 protein and Tie-2/Inhibitor III in the method, in order to search for possible drug candidates, as described by Chen et al. (col. 4, lines 32-38). Thus, Chen et al., in view of *In re Gulack*, motivate claims 21, 22, and 26.

Applicants submit the reference does not provide any suggestion or motivation to modify Chen et al. to arrive at a method of identifying compounds that inhibit a Tie-2 protein. This is found unpersuasive as modifications of Chen et al.'s reference was provided (col. 38, lines 2-5), as stated above. The fact that the coordinate data is non-functional descriptive material provides data that could be placed/modified into Chen et al.'s invention. Replacing Chen et al.'s non-descriptive material of the STAT protein with another type of protein, such as Tie-2, is a feasible modification. Applicants state that the invention is to be considered as a whole. The invention was considered as a whole, and due to the non-functional descriptive material present, the modifications of the Chen et al. invention would be considered obvious to one of ordinary skill in the art. Regarding *In re Gulack*, the atomic coordinates of the Tie-2 protein do not exhibit a functional interrelationship with the way in which computing processes are performed. The

computer processes act the same way on the Tie-2 protein as they would on Chen et al.'s STAT protein, demonstrating the non-functional descriptive material present in the instant invention.

The rejection of claims 21-27 is maintained under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (P/N 6,160,092), in view of *In re Gulack* (703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983)), *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594), and Ziegler (P/N 5,447,860).

The rejection is maintained and reiterated for reasons of record.

Chen et al. describe a method for identifying an agent that diminishes the activity of a protein (col. 4, lines 56-60). Chen et al. describe determining the three-dimensional structure of a compound based on structural coordinates obtained from X-ray crystallographic analysis of crystals (col. 4, lines 14-22). Chen et al. describe various binding domains of a protein (col. 6, lines 12-18 and col. 9, lines 56-64), interactive areas in these domains using crystal structure data (col. 10, lines 3-9) and catalytic sites (col. 14, lines 61-65). Chen et al. describe using computer modeling to select potential agents and contacting the agents with the protein (col. 4, col. 21-26). Chen et al. describe determining whether the agent affects the ability of the protein to induce expression of a gene that is operably under the control of a promoter containing the binding site for the protein (col. 4, lines 56-50). Chen et al. describe the potential modulator can be synthesized de novo or selected from a library of chemicals (col. 23, lines 13-24). Chen et al. describe that the proteins and core fragments thereof may be chemically synthesized (col. 19, lines 21-24) and modified (col. 5, lines 38-39). Chen et al. describe identifying potential modulators by screening a random peptide library and further modified using computer modeling

programs (col. 22, lines 51-59). Chen et al. do not describe the three-dimensional structure of the Tie-2 or Tie-2/Inhibitor III complex, various characteristics of the Tie-2 protein, or the amino acid sequence of SEQ ID NO: 1.

Even though the method described by Chen et al. does not specify that the active site was identified by the crystal structure coordinates and the three-dimensional model of the Tie-2 protein and Tie-2/Inhibitor III complex, the specific limitations of crystal structure coordinates and the three-dimensional model of the Tie-2 protein and Tie-2/Inhibitor III complex in this instant case do not distinguish the invention from the prior art in terms of patentability, because they are nonfunctional descriptive subject matter.

In re Gulack defines nonfunctional descriptive material to be descriptive material that is not functionally related to the substrate, in such a way that this descriptive material will not distinguish the invention from the prior art in terms of patentability. Also, the MPEP indicates that descriptive material unable to exhibit any functional interrelationship with the way in which computing processes are performed does not constitute a statutory process, machine, manufacture or composition (MPEP § 2106, section VI). Due to the fact that the coordinate data set derived from the crystal structure of the Tie-2 protein or Tie-2/Inhibitor III complex to develop three-dimensional models in the instant case are merely stored so as to be read or outputted by a computer without creating any functional interrelationship, either as part of the stored data or as part of the computing processes performed by the computer, this descriptive material alone does not impart functionality either to the data as structured, or to the computer.

Ziegler describes a polypeptide sequence of a receptor tyrosine kinase (Fig 1f-1h, residues 802-1124) that is identical to residues 802-1124 of SEQ ID NO: 1 of the instant

invention (see Sequence Match Listing) as stated in claim 27. Ziegler describes this amino acid sequence is from human cDNA (col. 4, lines 25-27) and can be found in mammalian sources (col. 6, line 41) as stated in claims 23 and 24. Ziegler describes a native, or wild-type, human ork protein (col. 5, lines 62-65). [It is interesting to note that Ziegler states ork and Tie proteins are distinctly different as presented in Figures 5a and 5b (col. 5, lines 15-26); however, the entire sequence in the instant invention shows that Tie-2 completely matches the ork sequence described by Ziegler.] Ziegler describes that ork can be used as a research tool for identifying ligands and assessing the biological effects of ligand binding (col. 17, lines 26-55) as stated in claim 22.

Since the sequences of ork (as stated by Ziegler) and Tie-2 (as stated in the instant invention) appear to be identical, *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) are hereby enforced.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second paragraph, first full paragraph).

As the invention of Chen et al. contains a method for identifying agents that interact with a protein and various modifications to their invention would be apparent to one of ordinary skill in the art (col. 38, lines 2-5), a person of ordinary skill in the art would have been motivated to include any crystalline protein already identified into this method in order to search for new

drugs (col. 3, lines 5-9). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the three-dimensional model of the Tie-2 protein (which has the inherent characteristics as presented by Ziegler) and Tie-2/Inhibitor III in the method, in order to search for possible drug candidates, as described by Chen et al. (col. 4, lines 32-38). Thus, Chen et al., in view of *In re Gulack, In re Best, In re Fitzgerald*, and Ziegler, motivate claims 21-27 in the instant invention.

Newly presented arguments in this 35 U.S.C. 103(a) rejection include that Ziegler describes the biological ligand of Tie-2 that binds to the extracellular domain as opposed to small ligands that bind to the catalytic domain of Tie-2. Instant claim 21, step (a) recites obtaining coordinates of a crystal that has the catalytic domain of a Tie-2 protein. It is noted that Applicants are claiming, in claim 21 step (a), atomic coordinates of an entire crystal that has the catalytic domain of a Tie-2 protein, not only the atomic coordinates of the catalytic domain of such a crystallized protein. With identical sequences, Applicants have not shown how Ziegler's ork and the instant application's Tie-2 differ.

The rejection of claims 21-27 is maintained under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (P/N 6,160,092), in view of Vikkula et al. (Cell, 1996, Volume 87, pages 1181-1190) and *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594).

The rejection is maintained and reiterated for reasons of record.

Chen et al. describe a method for identifying an agent that diminishes the activity of a protein (col. 4, lines 56-60). Chen et al. describe determining the three-dimensional structure of a compound based on structural coordinates obtained from X-ray crystallographic analysis of

crystals (col. 4, lines 14-22). Chen et al. describe various binding domains of a protein (col. 6, lines 12-18 and col. 9, lines 56-64), interactive areas in these domains using crystal structure data (col. 10, lines 3-9) and catalytic sites (col. 14, lines 61-65). Chen et al. describe using computer modeling to select potential agents and contacting the agents with the protein (col. 4, col. 21-26). Chen et al. describe determining whether the agent affects the ability of the protein to induce expression of a gene that is operably under the control of a promoter containing the binding site for the protein (col. 4, lines 56-50). Chen et al. describe the potential modulator can be synthesized de novo or selected from a library of chemicals (col. 23, lines 13-24). Chen et al. describe that the proteins and core fragments thereof may be chemically synthesized (col. 19, lines 21-24) and modified (col. 5, lines 38-39). Chen et al. describe identifying potential modulators by screening a random peptide library and further modified using computer modeling programs (col. 22, lines 51-59). Chen et al. do not describe the three-dimensional structure of the Tie-2 or Tie-2/Inhibitor III complex.

Vikkula et al. describe a three-dimensional structure of a domain location of Tie-2 receptor kinase (Figure 6). Vikkula et al. describe a GenBank accession number L06139 (see GenBank reference with both nucleic acid and polypeptide translation) which is nucleic acid sequence of human Tie-2 protein (page 1183, col. 2, first paragraph) that is 100% identical to the residues 802-1124 of the sequence in the instant invention (see Sequence Match Listing of encoded protein match). Vikkula et al. describe using wild-type and mutant Tie-2 cDNA in their research (page 1183, col. 2, second paragraph to page 1184, col. 1, second paragraph) as stated in claims 23-25 and 27. Although Vikkula et al. do not describe the atomic coordinates obtained

from a crystallized protein, as stated in claim 1 (lines 3-4), this limitation appears to be merely an additional measurement made of the same Tie-2 as described by Vikkula et al.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter that there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second paragraph, first full paragraph).

As the invention of Chen et al. contains a method for identifying agents that interact with a protein and various modifications to their invention would be apparent to an artisan of ordinary skill in the art (col. 38, lines 2-5), one of ordinary skill in the art would have been motivated to include any crystalline protein complex already identified into this method in order to search for new modulators (col. 3, lines 5-9). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the three-dimensional model of the Tie-2 protein (as stated by Vikkula et al.) in the method, in order to search for possible drug candidates, as described by Chen et al. (col. 4, lines 32-38). Thus, Chen et al., in view of Vikkula et al. and *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594), motivate claims 21-27 in the instant invention.

This rejection was not addressed by Applicants and is hereby maintained without further rebuttal.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

March 9, 2004

ARDIN H. MARSCHEL
PRIMARY EXAMINER